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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,551	09/27/2001	Muthiah Manoharan	ISIS-4847	3873

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	15

DATE MAILED: 04/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,551	MANOHARAN, MUTHIAH	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination

Applicant's request for reconsideration of the finality of the rejection of the last Office action mailed February 14, 2003 is persuasive and, therefore, the finality of that action is withdrawn.

In the final rejection mailed November 20, 2002, and in inadvertent error, independent claims 28-30 were not recited in maintaining the enablement rejection of record against claims 28-30 and 34-51. In response, applicant canceled remaining claims 34-51, in the belief that because claims 28-30 had not been rejected, that they were considered allowable. Applicants' cancellation was done despite the fact that the substance of the maintained rejection was clearly drawn to the independent claims. Furthermore, no indication of allowability had been issued at any point in prosecution history, and to the contrary, it was clearly the examiner's view in reading all rejections of record that applicant's response had not overcome any rejections in any Office action to date in the instant application. In order to correct the inadvertent error, a new Office action was issued and mailed February 14, 2003 that rejected all outstanding claims 28-30. The most recent version of the enablement rejection of February 14, 2003, which reiterated the old grounds of rejection that are of record, was made final; however, applicant is accorded the withdrawal of finality of said Office action to ensure fair and proper final disposal of the instant application.

Status of Claims/Amendments/Specification

In accordance with 37 C.F.R. 1.121(c)(2), applicants' request for re-entry of claims 34-51 is denied. A claim canceled by amendment (deleted in its entirety) may be reinstated only by a subsequent amendment presenting the claim as a new claim with a new claim number. See further M.P.E.P. § 608.01(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 28-30 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated gene inhibition *in vitro*, does not reasonably provide enablement for treating any animal with any disease associated with the overproduction of any protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the same reasons of record as originally set forth in the Office action mailed June 5, 2002.

Response to Arguments

Applicants have traversed the most recent rejection of the Office action dated February 14, 2003, by emphatically arguing that said claims omitted in obvious error in the Office action mailed November 20, 2002 were "by rule allowed" due to such omission, which should now be indicated in a Notice of Allowability. However, no indication of allowability was forwarded to applicant at any time in prosecution. No claim was indicated as allowable on the PTO-form 326

Office action summary. Furthermore, the rejection reiterated in the Office action containing the error was clearly drawn to the independent claims. Despite applicants' gross assertions that "by right" they are entitled to a resulting patent, no claim has ever been indicated as allowable. Applicants' insistence on gaining an issued patent from an acknowledged and corrected error by the Office is misguided; that some claims were not referred to in an Office action, a situation that has been corrected by the issuance of a new round of Office actions, does not in any way confer allowability to said claims.

Applicant supplies case law to fortify their allegation that a rejection once withdrawn automatically is "by rule" allowed. However, the cited case law does not by any stretch support applicants' conclusion, because, among other things, nowhere in the cited case law does it state that in a pending application, a rejection once withdrawn thus confers allowability. In fact the cited case concerns only the validity of issued patents (Paperless Accounting Inc. v. Bay Area Rapid Transit System, 804 F.2d 659, 231 USPQ (BNA) 649 (CAFC, 1986). Applicant is reminded that the instant application has not issued as a patent. Finally, even if for the sake of argument said claims had been indicated as allowable, which they weren't, applicant should be aware it is within the authority of the Office to withdraw claims once considered allowable should any issue come to light requiring the Office to take action. See M.P.E.P. § 706.04. To be clear, pending claims 28-30 are not allowed, as indicated in the final Office action mailed February 14, 2003, nor have they ever been indicated as allowed at any time in the prosecution of the instant application.

Regarding applicants' assertions that the claims of the instant invention are enabled, applicants repeatedly emphasize that although the references cited by the examiner express

doubts in the field of antisense therapy "in general", the examiner failed to provide specific evidence as to why Applicants' instant oligos "in particular" are not enabled. While it is true that there is no art teaching that applicants' instant oligos don't work *per se*, this is not the standard by which enablement is determined. Enablement is determined by analyzing the Wands factors, reiterated below:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Importantly, guidance must come from either the prior art, or from the specification. Because applicant has not supplied any examples of the claimed *in vivo* antisense-mediated treatment, or provided any other form of enabling disclosure from an analogous model system, one of skill is left with no guidance from the specification how to bridge the gap in using *in vitro* results to treating any disease *in vivo*. In other words, because of applicants' lack of specific guidance or relevant exemplification in the specification, it is impossible to comment on applicants' oligos "in particular" as demanded by applicant. Thus, one of skill can only turn to the prior art "in general" for guidance. As stated in previous Office actions, the state of the prior art is such that the efficacy of antisense oligos *in vivo* varies unpredictably from their efficacy *in vitro*, such that one cannot predict *a priori* which will work *in vivo* and which won't. One of skill in the art cannot simply demonstrate inhibition using cultured cells *in vitro,* apply a prophetic treatment regimen, and thereby treat any disease, as applicant argues.

Regarding the references supplied by the examiner that demonstrate the unpredictability of antisense-mediated therapy, applicant argues repeatedly that the examiner improperly reached the conclusion that the instant "invention lacks enablement for the simple reason that several review articles have expressed doubts in the field of antisense therapy." Again it is pointed out that unpredictability in the art is another Wands factor required for a proper analysis of enablement. Applicants' admission that the cited references express doubts in the field of antisense therapy is significant, and supports the examiner's conclusion of unpredictability in the art. Based on the doubts expressed in the cited references, which are review articles that appear in peer reviewed journals and thus are indicative of the state of the art as a whole, it was concluded that not only is the field of antisense related therapy unpredictable, but also reasoned why, particularly in view of applicant's broad claims and lack of guidance or relevant exemplification, this would necessarily lead to undue trial and error experimentation for one of skill in the art who tries to practice this invention as claimed.

Applicants' arguments broadly assert that the examiner has mischaracterized the state of the art of antisense drug discovery as being much more unpredictable than other drug discoveries, and further, that examiner imposed the extreme standard that "undue experimentation means no experimentation required for one skilled in the art". As a side note, applicant has supplied this quoted phrase in their response as if these were the actual words of the examiner. This is utterly untrue; no words to this effect have ever appeared in any Official action.

It is not clear from where applicants' have drawn the conclusion that the examiner cited much higher unpredictability in antisense drug discovery. This statement does not appear to be a

part of any Office action to date, and applicants' have not indicated from where in the record that this conclusion comes from. While it is true that only one antisense drug has ever been "discovered", in fact, the only mention of a comparison made between antisense drug development and other types of drug development came in a quotation from a review article, not an examiner's statement. Based on the professional opinion of the authors of the cited review articles, antisense technology suffers from its own unique unpredictabilities as outlined and specifically referenced in all previous Office actions, regardless of its relationship with other types of drug discoveries. The instant enablement rejection focused specifically on why predicting *in vivo* antisense efficacy from *in vitro* data is unpredictable. Contrary to applicants' assertion, the Office action did not compare and contrast broad trends in drug discovery based on drug type, because such an analysis is irrelevant to the real issue at hand, that is, inherent problems in predicting *in vivo* efficacy of antisense compounds based on *in vitro* inhibition data, which has specific, art recognized complications, outlined in previous Office actions, that applicants' arguments do not address with any particularity in approximately 15 pages of arguments. Finally, it is unclear what relevance such a comparison would reveal, when again, the issue at hand is the enablement of applicants' claims, not the enablement of drug discovery in general.

Applicants' have alternated between using the examiner cited references to support their case for enablement, while later criticizing the references as providing some statements that are "clearly false" because they fail to consider antisense drugs in clinical trials (Pg 9, 3rd line, March 28, 2003 after final communication). As it turns out, applicants' characterization of some authors' statements as clearly false is unfounded, since despite applicants' multiple citations of

clinical trials that were underway during the writings cited by the examiner, only one antisense drug has ever been shown to have therapeutic value as discussed below. Applicants' piecemeal breakdown of the examiner cited references are not convincing, because they fail to indicate where in these review articles it is shown that art of antisense therapeutics is in anyway predictable. Applicants' arguments rely on picking certain statements that support applicants' position while casting dispersions on other statements that undermine their position.

Moreover, applicants cite statements from the text of these articles and use these to derive conclusions favorable to applicants' view that are clearly inconsistent with the authors meaning. For example, applicants cite Braasch's opening statements wherein "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology" as only referencing past problems that, according to applicant, "have been solved". As applicants' evidence that these problems have been solved, applicants cite later in Braasch that "those skilled in the art know how to deliver antisense oligonucleotides into various organs of both animals and humans...", and concludes therefore that "...Braasch actually supports applicant's position that the instant claims are enabled". However, applicants' conclusion is seriously compromised when it is considered that distributing antisense into various tissues has never been supplied as a cause for lack of enablement, either in any Office action or reference cited by the examiner. It is well known that one of skill can inject oligonucleotides and observe their distribution into various tissues and organs. It is altogether different for one of skill in the art to observe said oligos crossing cell membranes, avoiding non-specific binding with cellular proteins, overcoming target secondary structures and bound transcription factors, and finally inhibiting the expression of the gene. These are the issues in the art that applicants' specification fails to resolve. Contrary to

applicants' statements, it is clear from the previous Office actions and from applicants' cited comment that these references indicate significant doubt as to the predictability antisense-related therapy.

Also, applicant is critical of the Office action because "out of the 16,986 references (in the art of antisense oligos), the instant Office action has focused on select statements in **five** references to characterize the entire state of the art" (emphasis in original). This argument glides over the reality that the examiner-cited references are general review articles that are peer-reviewed, and as such are focused on summarizing the state of the art as a whole. While it is not within the scope of the patent examination process to review all 16,986 articles cited by applicant, it is maintained that the review articles supplied by the examiner are indicative of the state of the art.

Applicants' counter with the submission of exhibits B-I, which allegedly support enablement. However, it is significant that each of exhibits B-D and G-I are authored by employees of the assignee of the instant application. Furthermore, exhibit E, Whitesall et al., use unmodified oligonucleotides, while applicants' invention is novel precisely for its phosphorothioate modifications. Such modifications are associated with non-specific binding to cellular proteins, as evidenced in the references supplied by the examiner, most notably Branch et al., wherein the authors state that "they (phosphorothioate modified oligos) bind avidly to many proteins, forming complexes with dissociation constants one to three orders of magnitude lower than those of phosphodiester ODNs" (i.e. unmodified ODNs). In regards to applicants exhibit H, the reference the reference of Cossum et al.; this is a review from 1991. It is interesting to note that the references supplied by the examiner, which applicants admit express

at least some doubt in the art of antisense therapeutics, range in age from 1996 to 2002. Furthermore, Branch in 1998 indicated that Krieg, a prominent scientist in the field, expressed doubts about such published reports of antisense efficacy, stating that "the estimate that many people have given me of the percentage of accurate published antisense papers ranges from 50% of them being accurate to 5% being accurate". It if for these reasons that Applicants submission is not considered a convincing demonstration of enablement. In summary, while applicants' review of the 16,986 references has revealed a few references that discuss individual successes that may have occurred *in vivo*, it is not argued that such irregular success has occurred. Applicant is reminded that at issue is whether or not such sporadic success is predictable. Based on the review articles that summarize the state of the art, it is the position of the examiner that the art is unpredictable.

Applicants argue that the examiner improperly requires an extreme standard whereby no experimentation should be necessary for enablement, and further, that the specification provides adequate disclosure for using *in vitro* inhibition data to provide enablement for *in vivo* therapeutic success. This is not adopted, because none of applicants' supplied references provide a meaningful blueprint for resolving the known obstacles in the art in using data obtained *in vitro* to predict *in vivo* therapeutic success, as discussed above and in previous Office actions. While applicant repeatedly argues that antisense gene inhibition is enabled, it is submitted that this is not relevant; it has been set forth that applicant is enabled for antisense mediated inhibition *in vitro*, it is applicants' claimed method of treatment of the *in vivo* whole animal that is not enabled. One would necessarily have to resort to trial and error experimentation to make such a leap from antisense in cultured cells to providing therapy, because no clear guidance in resolving

these issues are found in the prior artor within applicants specification as filed. Although applicants' arguments rely heavily on the FDA approval of one antisense drug (Fomiversin) and notes that "many others" are currently involved in clinical trials, it is noted that today in 2003, Fomiversin is still the only drug approved by the FDA, and that many of those drugs referenced by Tamm and also by applicants have failed and have been abandoned during said clinical trials as ineffective. Currently attached is a Reuter's article on a recent clinical trial failure (results announced March 17, 2003), where it is stated that "Isis currently makes the world's only commercial antisense drug--a treatment for a rare types of eye infection in AIDS patients. Many once promising antisense drugs have failed, including experimental therapies from Isis for HIV and genital warts" (this article is included to rebut applicants' arguments and does not constitute a new grounds of rejection). Moreover, fomiversin is not representative of any antisense treatment as encompassed in applicants' claims, because fomiversin only treats a rare disease and is injected directly into the eye. This drug thus achieves high local concentrations that help circumnavigate the problematic issue of crossing cell membranes in high enough quantity to attain gene inhibition. Applicants claims by contrast broadly seek to treat any disease with the instant oligos; presumably, most somatic diseases would not be as vulnerable to antisense administration as the eye is with fomiversin, rendering applicants' instant comparison with fomiversin of little relevance to the enablement of claims broadly seeking to treat any disease associated with overproduction of a protein.

Furthermore, applicants allege that the reference of Branch teaches that one of skill would know how to deliver antisense oligos into various organs in both animals and humans, and also that applicants' specification provides *in vivo* data, and that this should be viewed as proper

guidance. Applicants *in vivo* data is characterized in applicants arguments as showing "modulation of protein binding" (page 14 of March 28, 2003 after final). It should be clarified that all that has been shown is that applicants oligos have somewhat reduced non-specific binding to plasma proteins, and does not indicate that any modulation of any intended target has ever occurred. Furthermore, said *in vivo* data does not show any antisense mediated-inhibition at any point; applicants have shown only that they can inject oligos and later observe said oligos in tissues (not cells). Applicants imply here that delivery into an organ is equated with delivery across the cell membrane, to the mRNA target, and that inhibition has resulted. This implication is not true. While it may be routine to one of skill in the art to inject oligos and have them circulate to various organs, the references provided show that the additional steps of cell membrane traversal and target access to effect inhibition is altogether different, and indeed unpredictable. Thus, applicants' assertion is not agreed with. Regarding applicants *in vitro* data, the Office action provided that applicants' are enabled for *in vitro* methods; at issue is whether the *in vitro* data provides proper guidance for using the claimed oligos *in vivo*, which in the examiner's view, does not. Applicants allege that in pointing out known sources of unpredictability known in the art, that the office action requires data comparable in breadth to that required by the FDA". This is clearly a stretch, since discussion of enablement in the Office actions was directed primarily to the unpredictability in the art, and lack of guidance in the specification. Applicant is invited to indicate where in any Office action human trials are required, as implied by Applicant (e.g. "seems to require actual clinical data", page 14 of March 28, 2003 after final). No such requirement has ever been set forth nor is one being made now.

Applicant is invited to supply whatever evidence they feel is necessary to support their claim of enablement.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
April 23, 2003

JOHN L. LeGUYADER
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